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Fibrous Dysplasia of Bone

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Fibrous dysplasia of bone is a disorder of unknown etiology in which skeletal aberrations constitute the cardinal feature. The condition is often monostotic but may be polyostotic. The disorder may be accompanied by extraskeletal manifestations, such as abnormal cutaneous pigmentation and endocrinopathies, most commonly precocious puberty. Surgical therapy is recommended when bony deformities become substantial or when function is threatened.

Fibrous dysplasia is a benign disorder in which normal mineralized bone is progressively replaced by irregular trabeculae of immature, poorly mineralized fibrous tissue. This process is thought to be due to either arrested bone development at the immature stage of woven bone or a disturbance of postnatal lamellar bone remodeling. The proliferation of fibrous tissue may extend beyond the normal osseous boundaries and give rise to expansion, distortion or structural weakness of the affected bone. Although fibrous dysplasia has been observed in human skeletons for centuries, it was not recognized as a clinically distinct entity until 1937.[1,2] Lichtenstein[3] introduced the term "fibrous dysplasia" in 1938, and described the clinical aspects of the disorder.

Fibrous dysplasia accounts for 2.5 percent of all bone neoplasms and 7 percent of all benign bone tumors.[4] In 70 percent of patients, fibrous dysplasia is monostotic, involving a single bone; the polyostotic form of the disease accounts for about 30 percent of cases.[5] In the polyostotic form, a unilateral distribution is common.

The location of the lesions is variable, with the most common sites being the ribs, femur, tibia and humerus.[6-9] The prevalence of craniofacial involvement is 10 percent in monostotic disease and nearly 50 percent in polyostotic disease.[10] The disorder occurs primarily in children and young adults. Males and females are equally affected, although the McCune-Albright syndrome (polyostotic fibrous dysplasia, cutaneous pigmentation and precocious puberty) shows a female preponderance.[11]

Etiology

Fifty years after its original description, the etiology of fibrous dysplasia remains unknown. Lichtenstein and Jaffe[12] attributed the disease to an embryologic defect in the bone-forming mesenchyma. Schlumberger,[13] noting the proliferation of connective tissue in response to trauma, postulated that fibrous dysplasia might represent a disturbance of this post-traumatic reparative process. The relatively high prevalence of the disorder during the pubertal years and the reported expansion of these lesions during pregnancy raise the possibility of a hormonal link.[14] A viral infection of bone has also been suggested as the etiology.

Clinical Presentation

Fibrous dysplasia may present with a variety of manifestations and most often becomes evident in childhood during the period of greatest skeletal growth.[15] A painless bony swelling is the most common initial presentation. When the facial bones are involved, bony enlargement may produce asymmetry of the face, nasal obstruction or cranial nerve compression. Visual problems, facial paralysis and anosmia may also occur.[16,17] Involvement of the long bones may lead to weakening or bending of

the bone as well as pathologic fracture.[18] The pathognomonic "shepherd's crook" deformity may be seen when the proximal femur is affected (*Figure 1*).

Following skeletal maturation, the disease process may stabilize, but later in life quiescent lesions may reactivate and new lesions may occasionally develop. To our knowledge, complete spontaneous involution of fibrous dysplasia has never been reported.

BIOCHEMICAL PROFILE

The accelerated turnover of bone cells in fibrous dysplasia results in detectable biochemical abnormalities. Alkaline phosphatase, an enzyme found in osteoblasts, is elevated in 25 percent of patients with monostotic disease and in nearly 70 percent of patients with polyostotic disease.[15] The degree of elevation is thought to be directly proportional to the extent of the disease; during periods of exacerbation, the serum alkaline phosphatase level can be expected to rise. Hydroxyproline, an important component of collagen, is elevated in the urine of patients with extensive fibrous dysplasia.[19] Despite the increased metabolic activity of bone, most patients have normal serum concentrations of calcium and phosphate, which suggests that the rates of bone formation and bone resorption are closely coupled.

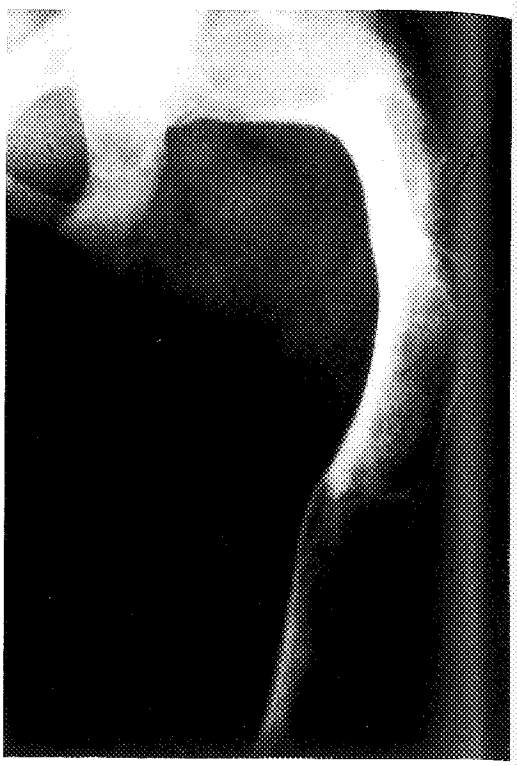
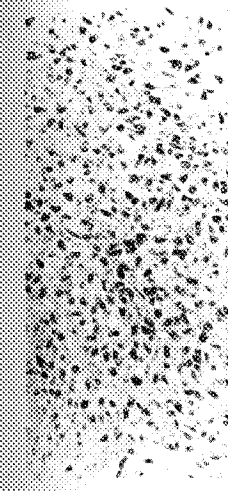


FIGURE 1. Radiograph of the femur, showing the classic "shepherd's crook" deformity of fibrous dysplasia.

Pathology and Histology

The progressive replacement of normal bone with fibrous tissue from within the medullary cavity produces a characteristic appearance. The lesions consist of rubbery, compressible grayish-white tissue of considerable vascularity, with a gritty texture and a thinned cortex. Pseudocysts filled with amber fluid are sometimes present.[6,20] Microscopically, strands of collagen are haphazardly arranged with a loosely or densely textured connective tissue stroma (*Figures 2a and 2b*). This characteristic woven, rather than lamellar, pattern differentiates fibrous dysplasia from other fibro-osseous disorders. The lesions are composed of an excessive amount of osteoid, indicating that bone mineralization is



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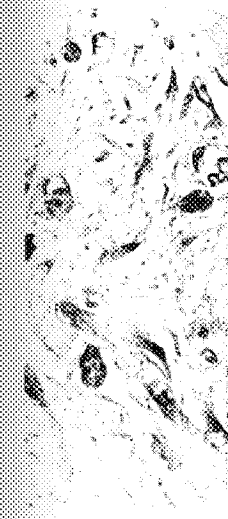

FIGURE 2B. Higher
fibrous proliferation.

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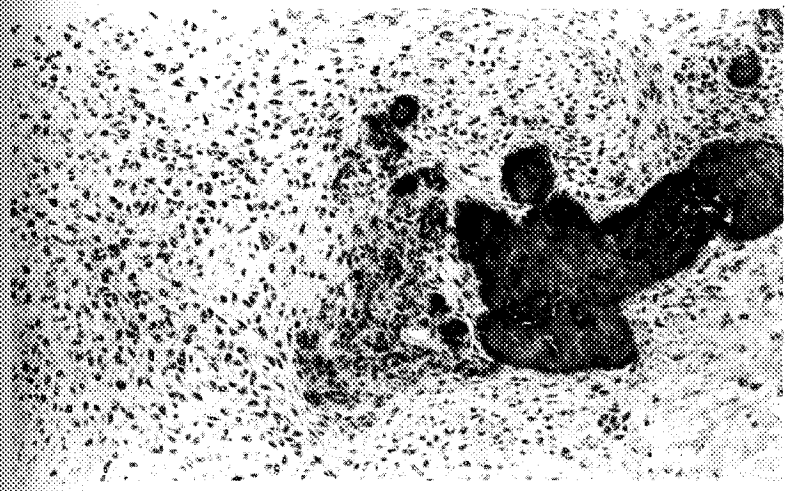

FIGURE 2A. Microscopic appearance of fibrous dysplasia of bone. The lesion consists of a proliferation of stellate and spindle-shaped fibroblasts with reticular collagen. Bizarre-shaped, immature bony tissue is present in association with this background of proliferating fibroblasts. (Hematoxylin-eosin, × 40)

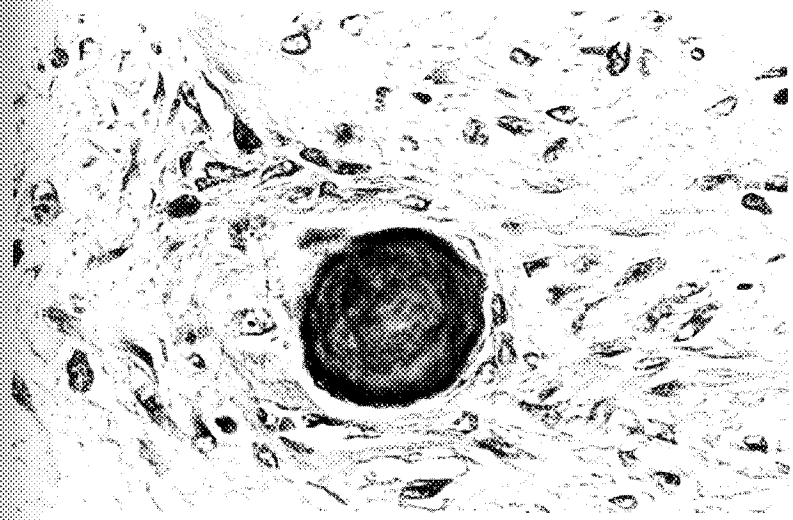

FIGURE 2B. Higher magnification showing spherical-shaped bone and cellular fibrous proliferation. (Hematoxylin-eosin, × 160)

impaired in the fibrous tissue. The number of osteoblasts is increased to 4.5 cells per mm^2; the normal quantity is 0.6 cells per mm^2.[19] Numerous spindle-shaped osteoblasts are present within the stroma, but the trabeculae show a lack of osteoblastic rimming. Osteocytic lacunae are wider than normal; however, the bone cells reveal a normal cytoarchitecture.[21]

Radiologic Features

Three radiographic patterns have been identified in fibrous dysplasia: pagetoid, sclerotic and cyst-like.[9] The pagetoid pattern is most common and is characterized by alternating areas of radiodensity and radiolucency. The sclerotic pattern displays bone expansion with a homogeneous radiodensity. The cyst-like pattern is characterized by round or oval radiolucent lesions with sclerotic borders (*Figure 3*). Regardless of the type, lesions almost always have poorly defined margins that blend gradually into normal bone.

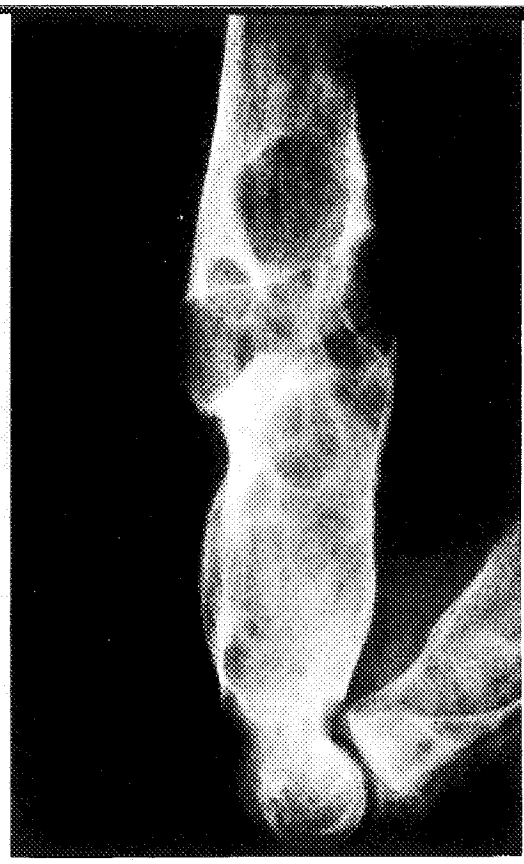

FIGURE 3. Cyst-like radiographic pattern of fibrous dysplasia. Multiple round and oval radiolucent areas, each with a sclerotic border, are seen in the humerus.

Radionuclide bone imaging reveals increased uptake in affected bone, making this study a useful screening test for additional sites of skeletal involvement (*Figure 4*).[22,23] Computed tomography performed

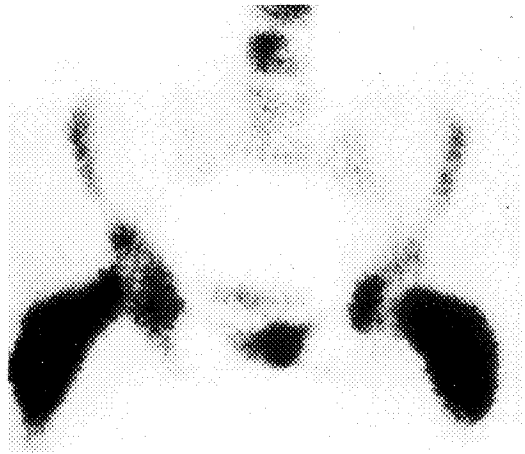

FIGURE 4. Technetium-99m radionuclide bone scan demonstrating increased uptake bilaterally over the proximal femurs, indicating active fibrous dysplasia.

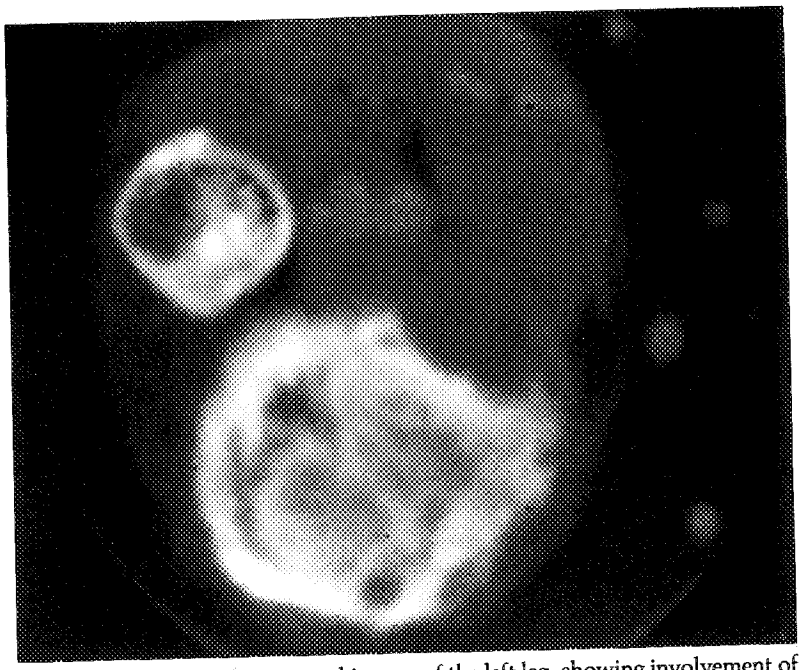

FIGURE 5. Computed tomographic scan of the left leg, showing involvement of the tibia with fibrous dysplasia. Note the areas of irregular contour and bony expansion.

FIGURE 6. Magnetic resonance image showing an area of increased signal, indicating fibrous dysplasia in the midtibial region.

in multiple planes can also provide useful localizing information (*Figure 5*).[24] The expansile nature of fibrous dysplasia can be readily seen on magnetic resonance imaging (*Figure 6*), although descriptions of the appearance of these lesions on magnetic resonance imaging are still sparse in the literature.[25,26] Correlation of findings from various radiographic studies with the pathologic and clinical data is mandatory for making the diagnosis of fibrous dysplasia.

Associated Disorders

Abnormal cutaneous pigmentation is the most common extraskeletal expression of fibrous dysplasia. In the monostotic form of the disease, pigmentation is an occasional finding, but it occurs in well over 50 percent of patients with polyostotic disease.[5] The skin lesions are small in number, variable in size and have irregular margins. Their color is light to dark brown. The most common sites of pigmentation are the back of the neck, the lower lumbar region, the face, the lips and the oral mucosa (*Figure 7*).[27]

Various endocrine abnormalities may develop in association with fibrous dysplasia. Precocious puberty is the most common, but hyperthyroidism, acromegaly, Cushing's disease, hyperparathyroidism and diabetes mellitus have also been reported.[28] While endocrinopathies occur primarily in patients with the polyostotic form of fibrous dysplasia, approximately 3 percent of all patients have an associated endocrinopathy.[29]

Treatment

The treatment of fibrous dysplasia has been almost exclusively surgical. In the past, surgical intervention was often delayed until after puberty, with the hope that the disease would become quiescent. However, because of multiple reports of persistence into later years, it is now recommended that surgery be performed as soon as the lesion

FIGURE 7. Cutaneous pigmentation on the back of the neck in a patient with craniofacial fibrous dysplasia.

becomes substantial or when important function is threatened.

Several surgical approaches have been used with varying success. Radical excision is being abandoned, since it is now recognized that removal of all dysplastic tissue is not needed to achieve a favorable result.

Simple contouring of facial and skull bones back to normal dimensions has proved quite effective. However, approximately one-fourth of patients so treated will require a repeat operation because of recurrence of bony enlargement.[30] A reduction in the rate of recurrence has been achieved with partial excision of the lesions followed by grafting with normal autologous bone.[31] Acrylic implants of methyl methacrylate have also worked well following excision. This method eliminates donor site morbidity and does not have the risk of possible regrowth of implanted tissue.

A new technique is currently being tested for reconstruction of craniofacial defects. Blocks of dysplastic bone are resected, contoured and then replaced as free grafts.[32]

A major hazard of surgery relates to the vascular character of the lesions. Severe bleeding requiring transfusion and the formation of postoperative intrabony hematomas have been encountered.[33]

Nonoperative treatment of fibrous dysplasia has been disappointing. Only five studies of medical treatment have been reported.[20,34-37] All of the trials involved treatment with calcitonin (Calcimar), a hormone that principally acts to suppress bone resorption through inhibition of osteoblasts. Although the patients showed a decrease in serum alkaline phosphatase levels and urinary hydroxyproline concentrations, radiographs and bone biopsies obtained at the end of the therapy did not demonstrate any structural improvement in the bone lesions.[34,35]

Malignant Change

Radiotherapy should never be used to treat fibrous dysplasia, both because of uniformly poor results and the greatly increased risk of malignant transformation after radiotherapy. The overall risk of malignant change is 0.5 percent (one in 200 patients),[38] but this rate increases 400 times in patients who have received radiotherapy.[32] The majority of the tumors are osteosarcomas; fibrosarcomas and chondrosarcomas develop less frequently. Clinical signs that signal sarcomatous transformation include pain, elevation of the serum alkaline phosphatase level, rapid growth of the lesion and invasion into cortical bone.

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